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Title: A stable solid dosage form comprising fenofibrate and an HMG CoA reductase inhibitor

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Patent- og Varemærkestyrelsen
Kongeriget Danmark

Patent- og Varemærkestyrelsen
Økonomi- og Erhvervsministeriet

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Susanne Morsing

PATENT- OG VAREMÆRKESTYRELSEN

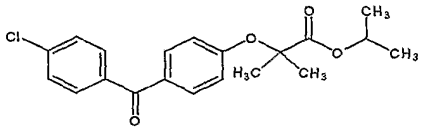
A STABLE SOLID DOSAGE FORM COMPRISING FENOFIBRATE AND AN HMG COA REDUCTASE INHIBITOR

The invention relates to a stable pharmaceutical composition comprising at least two active pharmaceutical ingredients, namely fenofibrate as a first ingredient and an HMG CoA reductase inhibitor or a derivative thereof as a second ingredient. More specifically, the invention relates to a single solid dosage form for oral administration comprising a solid fenofibrate composition and an HMG-CoA reductase inhibitor composition, preferably a statin compostion, the active substances being present in separate entities.

BACKGROUND OF THE INVENTION

Clinical guidelines indicate that not only fibrate therapy but also a combination therapy with e.g. fenofibrate and a statin should be the most effective means of cholesterol and lipid management. In fact, treatment with fenofibrate is often prescribed together with a statin as clinicians seem to prefer the use of e.g. fenofibrate due to its triglyceride-lowering and HDL-C increasing effects while a statin is used for its positive effects on lowering LDL-C and raising HDL-C. However, at present, such a combination therapy can only be achieved by the use of two separate products, i.e. the patient needs to take e.g. one fenofibrate tablet together with another tablet or capsule containing a statin.

Fenofibrate is chemically named 2-[4-(4-chlorobenzoyl]-2-methyl-propanoic acid, 1-methylethyl ester and has the following structural formula:



Fenofibric acid produces reductions in total cholesterol (total-C), LDL-C, apo-lipoprotein B, total triglycerides, and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apo-lipoprotein apoAI and apo AII. Fenofibrate acts as a potent lipid regulating agent offering unique and clinical advantages over existing products in the fibrate family of drug substances. Fenofibrate produces substantial reduction in plasma triglyceride levels in hypertriglyceridemic patients and in plasma cholesterol and LDL-C in hypercholesterolemic and mixed dyslipidemic patients.

Statins are HMG CoA reductase inhibitors. Useful statins include lovastatin, fluvastatin, rosuvastatin, pravastatin, atorvastatin and simvastatin.

International Application PCT/DK2004/000667 discloses Combination of fenofibrate and a statin in a single dosage form.

However, certain statins are known to be susceptible to degradation and/or oxidation when subjected to unfavorable physical and/or chemical conditions. Also, an optimized combination drug product may call for different release profiles for each of the active substances.

Accordingly, there is an unmet need for providing a single dosage form comprising fenofibrate and a statin in combination, in which the active pharmaceutical substances remain stable and wherein the active substances are provided in a formulation providing maximum bioavailablity and/or maximum therapeutic or pharmacological response.

SUMMARY OF THE INVENTION

The inventors have found that a drug combination product comprising fenofibrate and an HMG-CoA reductase inhibitor can advantageously be prepared as a single solid dosage form in such a manner that the two active drug substances are present in separate entities. Accordingly, the active substances are prevented from interaction; the active substances may independently of each other be provided in different release forms, i.e. in the form of immediate release, delayed release or controlled release compositions; and the combination drug product may have an increase stability due to the possibility of optimizing the formulations of each of the two active substances with respect to physical and/or chemical comditions.

Accordingly, in a first aspect the invention relates to a single solid dosage form for oral administration comprising a first solid pharmaceutical composition containing fenofibrate as the active substance and second solid pharmaceutical composition containing an HMG-CoA reductase inhibitor as the active substance, wherein the first and the second pharmaceutical composition are present in separate entities.

In a second aspect, the invention relates to a method of manufacturing the solid oral dosage form of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used herein, the term "active substance", "active pharmaceutical substance", "active ingredient" or "active pharmaceutical ingredient" means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the

body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and are present in the drug product in a modified form intended to furnish the specified activity or effect.

As used herein, the term "vehicle" means any solvent or carrier in a pharmaceutical product that has no pharmacological role. For example, water is the vehicle for xylocaine and propylene glycol is the vehicle for many antibiotics.

In the present context, the term "solid dispersion" denotes a drug or active ingredient or substance dispersed on a particulate level in an inert vehicle, carrier, diluent or matrix in the solid state, i.e. usually a fine particulate dispersion.

In the present context, the term "solid solution" denotes a drug or active ingredient or substance dissolved on a molecular level in an inert vehicle, carrier, diluent or matrix in the solid state.

As used herein, the term "analog" means a chemical compound that is structurally similar to another.

The term "drug" means a compound intended for use in diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.

In this context, the term "dosage form" means the form in which the drug is delivered to the patient. This could be parenteral, topical, tablet, oral (liquid or dissolved powder), suppository, inhalation, transdermal, etc.

As used herein, the term "bioavailability" denotes the degree means to which a drug or other substance becomes available to the target tissue after administration. In the present context, the term "suitable bioavailability" is intended to mean that administration of a composition according to the invention will result in a bioavailability that is improved compared to the bioavailability obtained after administration of the active substance(s) in a plain tablet; or the bioavailability is at least the same or improved compared to the bioavailability obtained after administration of a commercially available product containing the same active substance(s) in the same amounts. In particular it is desired to obtain quicker and larger and/or more complete uptake of the active compound, and thereby provide for a reduction of the administered dosages or for a reduction in the number of daily administrations. Further, pharmaceutical compositions of the invention may also reduce or negate the need for food to be takes simultaneously with the dosage form (in particular relevant for one or the active substances contained in a composition of the invention, namely fenofibrate) thereby allowing patients more freedom on when the drug is taken.

In this context, the term "medicine" means a compound used to treat disease, injury or pain. Medicine is designated "prophylactic," i.e. the art of preserving health, and "therapeutic" , i.e. the art of restoring health.

In the present context, the terms "controlled release" and "modified release" are intended to be equivalent terms covering any type of release of tacrolimus from a composition of the invention that is appropriate to obtain a specific therapeutic or prophylactic response after administration to a subject. A person skilled in the art knows how controlled release/modified release differs from the release of plain tablets or capsules. The terms "release in a controlled manner" or "release in a modified manner" have the same meaning as stated above. The terms include slow release (that results in a lower C_{max} and later t_{max}, but the half-life remains unchanged), extended release (that results in a lower C_{max}, later t_{max}, but apparent half-life is longer); delayed release (that result in an unchanged C_{max}, but lag time and, accordingly, t_{max} is delayed, and the half-life remains unchanged) as well as pulsatile release, burst release, sustained release, prolonged release, chrono-optimized release, fast release (to obtain an enhanced onset of action) etc. Included in the terms is also e.g. utilization of specific conditions within the body e.g., different enzymes or pH changes in order to control the release of the drug substance.

In this context, the term "erosion" or "eroding" means a gradual breakdown of the surface of a material or structure, for example of a tablet or the coating of a tablet.

In a first aspect, the invention relates to a single solid dosage form for oral administration comprising a first solid pharmaceutical composition containing fenofibrate as the active substance and second solid pharmaceutical composition containing an HMG-CoA reductase inhibitor as the active substance, wherein the first and the second pharmaceutical composition are present in separate entities. The HMG_CoA reductase inhibitor is a statin selected from the group consisting of atorvastatin, lovastatin, pravastatin, simvastatin, rosuvastatin, fluvastatin and pitavastatin.

In a preferred embodiment, the first solid pharmaceutical composition and/or the second solid pharmaceutical composition is in the form of granulate, granules, grains, beads or pellets, which are mixed and filled into capsules or sachets or are compressed to tablets by conventional methods. The granulate, granules, grains, beads or pellets containing the statin are optionally entero-coated or coated with a protective coating.

In another preferred embodiment, there is provided a tablet in which the first and second pharmaceutical compositions are present in at least two separate layers, i.e. a bilayer or multilayer tablet. The layers comprising the first and second pharmaceutical compositions may be separated by an intermediate, inactive layer, for example a layer comprising oneor more disintegrants.

In another aspect, the invention provides a method for preparing a single solid dosage form comprising a first solid pharmaceutical composition containing fenofibrate as the active substance and second solid pharmaceutical composition containing an HMG-CoA reductase

inhibitor as the active substance, the first and the second pharmaceutical composition being present in separate entities, which method comprising the steps of:

i) preparing the first solid pharmaceutical composition,

ii) preparing the second solid pharmaceutical composition, and

iii) compressing the first and second compositions into a multilayer tablet, the first and second compositions being present in separate layers.

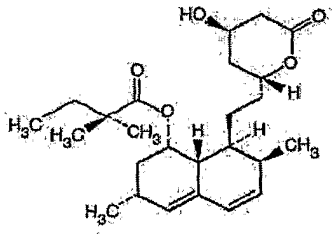
The active drug substances

A first drug or active substance of the dosage forms and pharmaceutical compositions of this invention is fenofibrate as described above or an analog thereof. However, it should be understood that this invention includes dosage forms and compositions comprising a mixture of two, three or even four different fibrates and/or fibric acids. Examples of other useful fibrates are bezafibrate, ciprofibrate, clinofibrate, clofibrate, etofylline, clofibrate, fenofibrate, gemfibrozil, pirifibrate, simfibrate and tocofibrate; particularly useful are gemfibrozil, fenofibrate, bezafibrate, clofibrate, ciprofibrate and active metabolites and analogues thereof including any relevant fibric acid such as fenofibric acid.

A second drug or active substance of the dosage forms and pharmaceutical compositions of this invention is an HMG-CoA reductase inhibitor or a derivative thereof, for example a statin selected from the group consiting of atorvastatin, fluvastatin, pravastatin, lovastatin, rosuvastatin and simvastatin and pharmaceutically acceptable salts thereof.

For example, simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2 *H* -pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1 *S* -[1(alpha),3(alpha),7(beta),8(beta)(2 *S* *,4 *S* *),-8a(beta)]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57.

Its structural formula is:



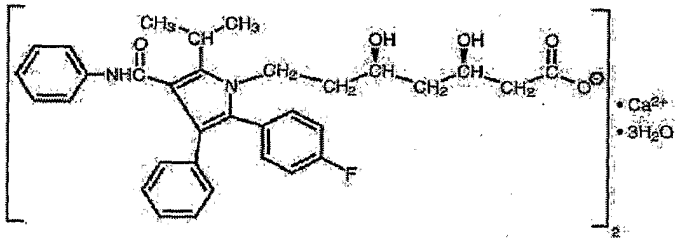
Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol.

Elevated plasma levels of total cholesterol (total-C), LDL-C, and apolipoprotein B (Apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of high-density lipoprotein cholesterol (HDL-C) and its transport complex, Apo A-I, are associated with decreased cardiovascular risk. High plasma

triglycerides (TG) and cholesterol-enriched TG-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. Elevated plasma TG is frequently found in a triad with low HDL-C and small LDL particles, as well as in association with non-lipid metabolic risk factors for CHD. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined. Simvastatin has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density lipoprotein (VLDL) and is catabolized predominantly by the high-affinity LDL receptor. Simvastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of simvastatin (estimated to be > 60% in man), the availability of drug to the general circulation is low.

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is (C33H34 FN2O5)2Ca•3H2O and its molecular weight is 1209.42.

Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol. The calcium salt has the following structural formula:



Atorvastatin is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug

absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is said to be similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is said to be the same regardless of the time of day of drug administration

Pharmaceutically acceptable excipients and additives

In the present context the terms "pharmaceutically acceptable excipient" are intended to denote any material, which is inert in the sense that it substantially does not have any therapeutic and/or prophylactic effect *per se*. Such an excipient may be added with the purpose of making it possible to obtain a pharmaceutical, cosmetic and/or foodstuff composition, which have acceptable technical properties. A particulate material or a solid dosage form according to the invention may contain one or more pharmaceutically acceptable excipients.

Examples of suitable excipients for use in a composition or solid dosage form according to the invention include fillers, diluents, disintegrants, binders, lubricants etc. or mixture thereof. As the composition or solid dosage form according to the invention may be used for different purposes, the choice of excipients is normally made taken such different uses into considerations. Other pharmaceutically acceptable excipients for suitable use are e.g. acidifying agents, alkalizing agents, preservatives, antioxidants, buffering agents, chelating agents, coloring agents, complexing agents, emulsifying and/or solubilizing agents, flavors and perfumes, humectants, sweetening agents, wetting agents etc.

Examples of suitable fillers, diluents and/or binders include lactose (e.g. spray-dried lactose, a-lactose, b-lactose, Tabletose®, various grades of Pharmatose®, Microtose® or Fast-Floc®), microcrystalline cellulose (various grades of Avicel®, Elcema®, Vivacel®, Ming Tai® or Solka-Floc®), hydroxypropylcellulose, L-hydroxypropylcellulose (low substituted), hydroxypropyl methylcellulose (HPMC) (e.g., Methocel E, F and K, Metolose SH of Shin-Etsu, Ltd, such as, e.g. the 4,000 cps grades of Methocel E and Metolose 60 SH, the 4,000 cps grades of Methocel F and Metolose 65 SH, the 4,000, 15,000 and 100,000 cps grades of Methocel K; and the 4,000, 15,000, 39,000 and 100,000 grades of Metolose 90 SH), methylcellulose polymers (such as, e.g., Methocel A, Methocel A4C, Methocel A15C, Methocel A4M), hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylene, carboxymethylhydroxyethylcellulose and other cellulose derivatives, sucrose, agarose, sorbitol, mannitol, dextrins, maltodextrins, starches or modified starches (including potato starch, maize starch and rice starch), calcium phosphate (e.g., basic calcium phosphate, calcium hydrogen phosphate, dicalcium phosphate hydrate), calcium sulfate, calcium carbonate, sodium alginate, collagen etc.

Specific examples of diluents are e.g., calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, microcrystalline cellulose, powdered cellulose, dextrans, dextrin, dextrose, fructose, kaolin, lactose, mannitol, sorbitol, starch, pregelatinized starch, sucrose, sugar etc.

Specific examples of disintegrants are e.g. alginic acid or alginates, microcrystalline cellulose, hydroxypropyl cellulose and other cellulose derivatives, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, starch, pregelatinized starch, carboxymethyl starch (e.g. Primogel® and Explotab®) etc.

Specific examples of binders are e.g., acacia, alginic acid, agar, calcium carrageenan, sodium carboxymethylcellulose, microcrystalline cellulose, dextrin, ethylcellulose, gelatin, liquid glucose, guar gum, hydroxypropyl methylcellulose, methylcellulose, pectin, PEG, povidone, pregelatinized starch etc.

Glidants and lubricants may also be included in the second composition. Examples include stearic acid, magnesium stearate, calcium stearate or other metallic stearate, talc, waxes and glycerides, light mineral oil, PEG, glyceryl behenate, colloidal silica, hydrogenated vegetable oils, corn starch, sodium stearyl fumarate, polyethylene glycols, alkyl sulfates, sodium benzoate, sodium acetate etc.

Other excipients which may be included in a composition or solid dosage form of the invention are e.g., flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents, absorption enhancing agents, agents for modified release etc.

Other additives in a composition or a solid dosage form according to the invention may be antioxidants like e.g. ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, potassium metabisulfite, propyl gallate, sodium formaldehylde sulfoxylate, sodium metabisulfite, sodium thiosulfate, sulfur dioxide, tocopherol, tocopherol acetate, tocopherol hemisuccinate, TPGS or other tocopherol derivatives, etc. The carrier composition may also contain e.g., stabilising agents. The concentration of an antioxidant and/or a stabilizing agent in the carrier composition is normally from about 0.1 % w/w to about 5% w/w.

A composition or solid dosage form according to the invention may also include one or more surfactants or substances having surface-active properties. It is contemplated that such substances are involved in the wetting of the slightly soluble active substance and thus, contributes to improved solubility characteristics of the active substance. Suitable surfactants for use in a composition or a solid dosage form according to the invention are surfactants such as, e.g., hydrophobic and/or hydrophilic surfactants as those disclosed in WO 00/50007 in the name of Lipocine, Inc.

Specific examples of suitable surfactants are polyethoxylated fatty acids such as, e.g., fatty acid mono- or diesters of polyethylene glycol or mixtures thereof such as, e.g., mono – or diesters of polyethylene glycol with lauric acid, oleic acid, stearic acid, myristic acid, ricinoleic acid, and the polyethylene glycol may be selected from PEG 4, PEG 5, PEG 6, PEG 7, PEG 8, PEG 9, PEG 10, PEG 12, PEG 15, PEG 20, PEG 25, PEG 30, PEG 32, PEG 40, PEG 45, PEG 50, PEG 55, PEG 100, PEG 200, PEG 400, PEG 600, PEG 800, PEG 1000, PEG 2000, PEG 3000, PEG 4000, PEG 5000, PEG 6000, PEG 7000, PEG 8000, PEG 9000, PEG 1000, PEG 10,000, PEG 15,000, PEG 20,000, PEG 35,000, polyethylene glycol glycerol fatty acid esters, i.e. esters like the above-mentioned but in the form of glyceryl esters of the individual fatty acids; glycerol, propylene glycol, ethylene glycol, PEG or sorbitol esters with e.g., vegetable oils like e.g., hydrogenated castor oil, almond oil, palm kernel oil, castor oil, apricot kernel oil, olive oil, peanut oil, hydrogenated palm kernel oil and the like, polyglycerized fatty acids like e.g., polyglycerol stearate, polyglycerol oleate, polyglycerol ricinoleate, polyglycerol linoleate, propylene glycol fatty acid esters such as, e.g., propylene glycol monolaurate, propylene glycol ricinoleate and the like, mono- and diglycerides like e.g. glyceryl monooleate, glyceryl dioleae, glyceryl mono- and/or dioleate, glyceryl caprylate, glyceryl caprate etc.; sterol and sterol derivatives; polyethylene glycol sorbitan fatty acid esters (PEG-sorbitan fatty acid esters) such as esters of PEG with the various molecular weights indicated above, and the various Tween® series (from ICI America, Inc.); polyethylene glycol alkyl ethers such as, e.g., PEG oleyl ether and PEG lauryl ether; sugar esters like e.g. sucrose monopalmitate and sucrose monolaurate; polyethylene glycol alkyl phenols like e.g. the Triton® X or N series (Union Carbide Chemicals & Plastics Technology Corporation); polyoxyethylene-polyoxypropylene block copolymers such as, e.g., the Pluronic® series from BASF Aktiengesellschaft, the Synperonic® series from ICI America, Inc., Emkalyx , Lutrol® from BASF Aktiengesellschaft, Supronic etc. The generic term for these polymers is "poloxamers" and relevant examples in the present context are Poloxamer 105, 108, 122, 123, 124, 181, 182, 183, 184, 185, 188, 212, 215, 217, 231, 234, 235, 237, 238, 282, 284, 288, 331, 333, 334, 335, 338, 401, 402, 403 and 407; sorbitan fatty acid esters like the Span® series (from ICI) or Arlacel® series (from ICI) such as, e.g., sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate etc.; lower alcohol fatty acid esters like e.g., oleate, isopropyl myristate, isopropyl palmitate etc.; ionic surfactants including cationic, anionic and zwitterionic surfactants such as, e.g., fatty acid salts, bile salts, phospholipids, phosphoric acid esters, carboxylates, sulfates and sulfonates etc.

When a surfactant or a mixture of surfactants is present in a composition or a solid dosage form of the invention, the concentration of the surfactant(s) is normally in a range of from about 0.1 – 80% w/w such as, e.g., from about 0.1 to about 20% w/w, from about 0.1 to

about 15% w/w, from about 0.5 to about 10% w/w, or alternatively, from about 0.10 to about 80% w/w such as, e.g. from about 10 to about 70% w/w, from about 20 to about 60% w/w or from about 30 to about 50% w/w.

In a specific aspect of the invention, the at least one of the one or more pharmaceutically acceptable excipient is selected from the group consisting of silica acid or a derivative or salt thereof including silicates, silicon dioxide and polymers thereof; magnesium aluminosilicate and/or magnesium aluminometasilicate, bentonite, kaolin, magnesium trisilicate, montmorillonite and/or saponite.

Solid dosage form design

Method of manufacture

The first solid composition of the invention may be prepared by any method suitable for incorporation of poorly water-soluble active substances. The pharmaceutical compositions may be prepared by any convenient method such as, e.g. granulation, mixing, spray drying etc. A particularly useful method is the method disclosed in Applicants' co-pending international application published as WO 03/004001, which describes a process for preparation of particulate material by a controlled agglomeration method, i.e. a method, which enables a controlled growth in particle size. The method involves spraying a first composition comprising the active substance and a vehicle in liquid form onto a solid carrier. Normally, the vehicle has a melting point of at least 5°C, but the melting point must indeed be below the melting point of the active substance. In the present invention, the melting point of the vehicle and should not exceed 250°C.

It is within the skills of the average practitioner to select a suitable vehicle being pharmaceutical acceptable, capable of dispersing or fully or at least partly dissolving the active substance and having a melting point in the desired range using general knowledge and routine experimentation. Suitable candidate for carriers are described in WO 03/004001, which is herein incorporated by reference.

In the present context, suitable vehicles are e.g., those mentioned as vehicles or as oily materials as well as those disclosed in WO 03/004001. An advantage of using the controlled agglomeration method described in WO 03/004001 is that it is possible to apply a relatively large amount of a liquid system to a particulate material without having an undesirable growth in particle size. Accordingly, in one embodiment of the invention, the particulate material of a pharmaceutical composition has a geometric weight mean diameter d_{gw} of ≥ 10 mm such as, e.g. ≥ 20 mm, from about 20 to about 2000, from about 30 to about 2000, from about 50 to about 2000, from about 60 to about 2000, from about 75 to about 2000 such as, e.g. from about 100 to about 1500 mm, from about 100 to about 1000 mm or from about 100 to about 700 mm, or at the most about 400 mm or at the most 300 mm such

as, e.g., from about 50 to about 400 mm such as, e.g., from about 50 to about 350 mm, from about 50 to about 300 mm, from about 50 to about 250 mm or from about 100 to about 300 mm.

The first compositions of the invention are preferably formed by spray drying techniques, controlled agglomeration, freeze-drying or coating on carrier particles or any other solvent removal process. The dried product contains the active substance present preferably in dissolved form either fully dissolved as a solid solution or partly dissolved as a solid dispersion including a molecular dispersion and a solid solution.

However, the first composition of the invention are preferably manufactured by a method comprising the steps of:

i) bringing the vehicle in liquid form, i.e. melting the vehicle if solid at room temperature,

ii) maintaining the liquid vehicle at a temperature below the melting point of the fibrate,

iii) dissolving the desired amount of fibrate in the vehicle,

iv) spraying the resulting solution onto a solid carrier having a temperature below the melting point of the vehicle,

v) mechanically working the resulting composition to obtain particles, i.e. a particulate material, and

vi) optionally subjecting the particulate material to conventional methods for preparing solid dosage forms.

The second solid compositions may be prepared in a similar manner or may be prepared by conventional wet granulation techniques.

In an important embodiment of the invention, at least part of the fibrate is present in the composition in the form of a solid dispersion including a molecular dispersion and a solid solution. Normally, about 10% or more such as, e.g., about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more such as, e.g., about 95% or more or about 100% w/w of either the fibrate or the statin is present in the vehicle in the form of a solid dispersion, provided that at least about 80% w/w of the total amount of active substances is dissolved in the vehicle.

A solid dispersion may be obtained in different ways e.g., by employing organic solvents or by dispersing or dissolving the active substance in another suitable medium (e.g. an oily material that is in liquid form at room temperature or at elevated temperatures). Solid dispersions (solvent method) are prepared by dissolving a physical mixture of the active substance (e.g. a drug substance) and the carrier in a common organic solvent, followed by evaporation of the solvent. The carrier is often a hydrophilic polymer. Suitable organic solvents include pharmaceutical acceptable solvent in which the active substance is soluble

such as methanol, ethanol, methylene chloride, chloroform, ethylacetate, acetone or mixtures thereof.

Suitable water-soluble carriers include polymers such as polyethylene glycol, poloxamers, polyoxyethylene stearates, poly-epsilon-caprolactone, polyvinylpyrrolidone (PVP), polyvinylpyrrolidone-polyvinylacetate copolymer PVP-PVA (Kollidon VA64), poly-methacrylic polymers (Eudragit RS, Eudragit RL, Eudragit NE, Eudragit E) and polyvinyl alcohol (PVA), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), methyl cellulose, and poly(ethylene oxide) (PEO).

Polymers containing acidic functional groups may be suitable for solid dispersions, which release the active substance in a preferred pH range providing acceptable absorption in the intestines. Such polymers may be one ore more selected from the group comprising hydroxypropyl methylcellulose phtalate (HMPCP), polyvinyl acetate phtalate (PVAP), hydroxypropylmethylcellulose acetate succinate (HPMCAS), alginate, carbomer, carboxymethylcellulose, methacrylic acid copolymer (Eudragit L, Eudragit S), shellac, cellulose acetate phthalate (CAP), starch glycolate, polacrylin, methyl cellulose acetate phtalate, hydroxypropyulcellulose acetate phthalate, cellulose acetate terephtahalate, cellulose acetate isophthalate and cellulose acetate trimellitate.

The weight ratio of active substance to polymer may be in a range of from about 3:1 to about 1:20. However, narrower ranges of from about 3:1 to about 1:5, such as, e.g., from about 1:1 to about 1:3 or about may also be used.

Apart from using the organic solvent based method, solid dispersion or solid solutions of one or more fibrates may be also obtained by dispersing and/or dissolving the active compound in the carrier composition used in the controlled agglomeration method. Stabilizing agents etc. may be added in order to ensure the stability of the solid dispersion/solution.

Fenofibrate and a statin may be combined in the composition or solid dosage form of the invention by using the following method: A fenofibrate granulate is prepared as disclosed in International Application PCT/DK2004/000667 and example 11 herein. A statin granulate is prepared in the same manner as the fenofibrate granulate, i.e. by dissolving or dispersing simvastatin in a suitable vehicle such as the vehicle used for dissolving/dispersing fenofibrate and spraying the dispersion onto a suitable carrier to obtain a granulate. The two granulates are mixed and either compressed into tablets or filled into hard gelatine capsules or sachets. The statin granulate may be entero-coated or coated with a protective coating, for example a film-forming polymer and stabilizers (antioxidants). The tablets might be sub-coated with a film-forming polymer before coating with the statin suspension below.

Examples of film polymers include water soluble agents such as hydroxypropylmethylcellulose, Metolose® (HPMC), hydroxypropylmethylcellulose, Klucel®

(HPC), polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP) or combinations of PVA and PVP (Kollicoat® IR) and acid soluble acrylic polymer (Eudragit E, soluble in gastric juice). Examples of antioxidants includes butylhydroxyanisol (BHA), ascorbyl palmitate, ascorbic acid or combinations of BHA, ascorbyl palmitate and citric acid.

Wetting and pH adjusting agent might be included in the coating suspension

Coating of the statin composition is performed in conventional coating equipment such as drum coater, perforated vessel or fluidized bed (Wurster insert).

Solid dosage forms

A solid dosage form according to the invention may be a single unit dosage form or it may in the form of a polydepot dosage form contain a multiplicity of individual units such as, e.g., pellets, beads and/or granules.

Usually, a pharmaceutical composition or a solid dosage form of the invention is intended for administration via the oral, buccal or sublingual administration route.

The invention also relates to the above-mentioned presentation form. Within the scope of the invention are compositions/solid dosage forms that are intended to release the active substance in a fast release, a delayed release or modified release manner.

A solid dosage form according to the present invention comprises a pharmaceutical composition in particulate form as described above. The details and particulars disclosed under this main aspect of the invention apply *mutatis mutandis* to the other aspects of the invention. Accordingly, the properties with respect to increase in bioavailability, therapeutic and/or pharmacological response, changes in bioavailability parameters, reduction in adverse food effect as well as release of one or more fibrates etc. described and/or claimed herein for pharmaceutical compositions in particulate form are analogues for a solid dosage form according to the present invention.

The solid dosage form of the invention, i.e. in unit dosage form, comprises comprises from about 130 to about 170 mg of fenofibrate and from about 5 to about 80 mg of statin or a pharmaceutically acceptable salt thereof.

The solid dosage forms of the invention are very stable. For example, the fibrate is present in an amount of at least about 90%, or at least about 95%, or at least about 100%, relative to the amount prior to storage, when assayed after 3 months of storage at a temperature of about 40°C and a relative humidity of about 75%. Also, the physical stability is very high as can be seen from the Examples below.

The solid dosage form according to the invention is obtained by processing the particulate material according to the invention by means of techniques well-known to a person skilled in the art. Usually, this involves further addition of one or more of the pharmaceutically acceptable excipients mentioned herein.

The composition or solid dosage form according to the invention may be designed to release fenofibrate and/or simvastatin in any suitable manner provided that the increase in bioavailability is maintained. Thus, the active substance(s) may be released relatively fast in order to obtain an enhanced on-set of action, it may be released so as to follow zero or first order kinetics or it may be released in a controlled or modified manner in order to obtain a predetermined pattern of release. Plain formulations are also within the scope of the present invention.

The composition or solid dosage form according to the invention may also be coated with a film coating, an enteric coating, a modified release coating, a protective coating, an anti-adhesive coating etc.

A solid dosage form according to the invention may also be coated in order to obtain suitable properties e.g. with respect to release of the active substance. The coating may be applied on single unit dosage forms (e.g. tablets, capsules) or it may be applied on a polydepot dosage form or on its individual units.

Suitable coating materials are e.g. methylcellulose, hydroxypropylmethyl-cellulose, hydroxypropylcellulose, acrylic polymers, ethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinylalcohol, sodium carboxymethylcellulose, cellulose acetate, cellulose acetate phthalate, gelatin, methacrylic acid copolymer, polyethylene glycol, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, zein.

Plasticizers and other ingredients may be added in the coating material. The same or different active substance may also be added in the coating material.
The pharmaceutical composition or a solid dosage form according to the invention is designed to release the fibrate in a suitable manner.

Other aspects of the invention

A pharmaceutical composition or a solid dosage form according to the invention is designed to release the fibrate in a suitable manner. Specific release patterns as well as specific absorption patterns are mentioned below.

In specific embodiments, the fibrate and/or the statin is released from the composition within about 2 hours such as, e.g., within about 1.5 hours or within about 1 hour after oral administration, and/or about 50% w/w or more of the fibrate and/or the statin is released from the composition within about 30 min after oral administration, and/or about 50% w/w or more of the fibrate and/or the statin is released from the composition within about 20 min after oral administration, and/or about 60% w/w or more of the fibrate is released from the composition within about 1.5 hours after oral administration, and/or about 60% w/w or more of the fibrate and/or the statin is released from the composition within

about 1 hour after oral administration, and/or about 70% w/w or more of the fibrate and/or the statin is released from the composition within about 1.5 hours after oral administration, and/or about 70% w/w or more of the fibrate and/or the statin is released from the composition within about 1 hour after oral administration, and/or about 85% w/w or more of the fibrate and/or the statin is released from the composition within about 45 min when tested in an *in vitro* dissolution test according to USP dissolution test (paddle) employing water as dissolution medium, 100 rpm and a temperature of about 37 °C.

In another embodiment about 50% w/w or more of the fibrate and/or the statin is released from the composition within about 20 min, 15 min or 10min, and/or about 60% w/w or more of the fibrate and/or the statin is released from the composition within about 20 min or 15 min, and/or about 70% w/w or more of the fibrate and/or the statin is released from the composition within about 20 min or 15 min, when tested in an *in vitro* dissolution test according to USP dissolution test (paddle) employing water as dissolution medium, 100 rpm and a temperature of about 37 °C.

In a still further embodiment about 50% w/w or more of the fibrate and/or the statin contained in the composition is absorbed within about 8 hours, 7 hours, 6 hours or 5 hours, and/or about 60% w/w or more of the fibrate and/or statin contained in the composition is absorbed within about 8 hours or 7 hours after oral administration, and/or about 60% w/w or more of the fibrate contained in the composition is absorbed within about 7 hours after oral administration, and/or about 70% w/w or more of the fibrate contained in the composition is absorbed within about 8 hours or 7 hours after oral administration.

The details and particulars disclosed under this main aspect of the invention apply *mutatis mutandis* to the other aspects of the invention. Accordingly, the properties with respect to increase in bioavailability, changes in bioavailability parameters, reduction in adverse food effect as well as release of one or more fibrates etc. described and/or claimed herein for pharmaceutical compositions in particulate form are analogues for a solid dosage form according to the present invention.

Materials and methods

Materials

Fenofibrate (supplied by Sigma)

Lactose monohydrate 200 mesh (from DMV)

Granulated silicium oxide, Aeroperl® 300, (Degussa)

Polyethylene glycol 6000, Pluracol® E6000 (from BASF)

Poloxamer 188, Pluronic® F-68 (from BASF)

Glyceryl monostearate, Rylo® MD50, (from Danisco Cultor), Ph.Eur.

Avicel PH200 (microcrystalline cellulose) (from FMC)

Magnesium stearate

Tablets, capsules or granules may be enteric coated with different types of polymers such as hydroxypropylmethylcellulose acetate succinate (Aqoat), cellulose acetate phthalate CAP, hydroxypropylmethylcellulose phtalate HPMCP or methacrylic acid copolymers such as Eudragit L30D, Eudragit 100/S, Eudragit 100/L.

Equipment

Laboratory scale fluid bed equipment: Strea-1.

The melt feed unit is a prototype composed of separate units for heating of air supplies for the atomizer, pressure tank and feeding tube. Granulate was sieved manually and mixed with extragranular excipients in a Turbula mixer.

Tablet compression was performed on a multilayer (bi-layer) tablet machine.

Methods

The fenofibrate drug may be dissolved into the melted vehicle(s) and applied on the particulate carrier(s) as follows:

The vehicle(s) was melted in a beaker placed in a microwave oven. The beaker was transferred to a temperature controlled heating plate supplied with magnetic stirring. Fenofibrate was dissolved slowly in the melt at a temperature of 75 °C under magnetic stirring. The hot solution was transferred to the pressure tank for melt spray application onto the carrier in the fluid bed. The granulate product was discharged from the fluid bed and sieved through sieve 0.7 mm or 1.0 mm manually. The sieved product was blended with magnesium stearate for 0.5 min in a Turbula mixer. If an extragranular phase has to be incorporated, the extragranular phase was premixed with the granulate in 3 minutes in a Turbula mixer.

Threshold Test

The test involves determination of flowability according to the method described in Ph.Eur. by measuring the flow rate of the material out of a funnel with a nozzle diameter of 10.0 mm.

Viscoleo (medium chain triglycerides MCT; Miglyol 812 N from Condea) was added to 100 g of the solid pharmaceutically acceptable material to be tested for use according to the invention and mixed manually. The mixture obtained was sieved through sieve 0.3 mm to assure a homogenous mixture. The oil was added successively until a flow of 100 g of the mixture could not flow through the nozzle. If the material to be tested has a high bulk volume

(e.g. like that of Aeroperl 300) only 50 g of the mixture is used when testing these blends. The maximal concentration of oil where flow of material could be obtained is called the Threshold Value (given as % w/w).

Release Test

A fat-soluble colorant Sudan II (BDH Gur®) obtained from BDH VWR International 14.3 mg was dissolved in 50.0 g viscoleo (fractionated medium chain triglycerides).

10 g of the oil was added to 10.0 g of the solid pharmaceutically acceptable material to be tested for use according to the present invention and mixed until the oil was fully absorbed in the solid material. The mixture was subsequently sieved through sieve 0.3 mm to achieve a homogeneous mixture.

1.00 g of the mixture was transferred to a centrifugal tube and 3.00 ml of water was added. The suspension was mixed in a blood sample turner for 1 hour and subsequently centrifuged for 10 minutes at 5000 rpm. The upper phase of oil and water was transferred carefully to a beaker and the water was evaporated in an oven at 80 °C until constant weight. The amount of oil released from the solid material was calculated on basis of the weight of the remaining after evaporation of the water phase.

Disintegration Test

The disintegration time was determined according to the method described in to Ph. Eur.

Dissolution Test

The test was performed in accordance with Ph. Eur 2.9.3 using the paddle apparatus. The quantification was performed using HPLC with UV-detection.

Medium:	900 ml water with 0.75 % sodium lauryl sulfate (SLS)
Rotation speed:	50 rpm
Temperature:	37°C
Sampling time:	10, 20, 30, 45 and 60 minutes
Acceptance criteria:	> 75 % at 45 minutes (for the stability study)

Determination of Flowability

The flowability was determined according to the method described in Ph.Eur. measuring the flow rate of the material out of a funnel with a nozzle diameter of 10.0 mm.

Determination of weight variation

The tablets prepared in the Examples herein were subject to a test for weight variation performed in accordance with Ph. Eur.

Determination of average tablet hardness

The tablets prepared in the Examples herein were subject to at test for tablet hardness employing Schleuniger Model 6D apparatus and performed in accordance with the general instructions for the apparatus.

Determination of solid solution

According to the present invention, the fibrate is dissolved in a vehicle. In order to substantiate this, a test involving differential scanning calometry is performed. The test is performed on the particulate composition, solid dosage form or mixture of vehicle and fibrate (after the solid solution is supposed to form). Standard DSC equipment connected to a PC is used.

Sample size: 10 mg in alu pans

Heating rate: 5°C /min from 27°C to 110°C

Evaluation: The fibrate and/or statin are considered to be in dissolved state or non-crystalline if neither fibrate nor statin endoterm peaks are observed and if the melting intervals do not significantly shift compared with the vehicle alone.

Determination of geometric weight mean diameter d_{gw}

The geometric weight mean diameter was determined by employment of a method of laser diffraction dispersing the particulate material obtained (or the starting material) in air. The measurements were performed at 1 bar dispersive pressure in Sympatec Helos equipment, which records the distribution of the equivalent spherical diameter. This distribution is fitted to a log normal volume-size distribution.

When used herein, "geometric weight mean diameter" means the mean diameter of the log normal volume-size distribution.

This invention may be embodied in other forms or carried out in other ways without departing from the spirit or essential characteristics thereof. The present disclosure is therefore to be considered as in all aspects illustrate and not restrictive, and all changes which come within the meaning and range of equivalency are intended to be embraced therein.

EXAMPLE 1

Preparation of fenofibrate granulate

The granulate was prepared as described above under Methods and in International Application PCT/DK2004/000667, which is incorporated by reference in its entirety:

Substance	Ingredient	%	mg
Drug	Fenofibrate	19.6	160.00
Carrier	Lactose	43.6	356.50
Vehicle	PEG 6000	25.4	208.20
Vehicle	Poloxamer 188	10.9	89.20
Excipient	Magnesium stearate	0.5	4.10
		100.0	818.00

EXAMPLE 2

Preparation of simvastatin granulate

The following statin granulate was prepared using the same method as disclosed in example 1:

Substance	Ingredient	%	mg
Drug	Simvastatin	6.7	10.00
Carrier	Lactose 200 mesh	33.3	50.00
Vehicle	PEG 6000	44.0	66.00
Vehicle	Poloxamer 188	14.7	22.00
Excipient	Magnesium stearate	1.3	2.00
		100.0	150.00

EXAMPLE 3

Preparation of atorvastatin granulate

The following statin granulate was prepared using the same method as disclosed in ex. 1:

Substance	Ingredient	%	mg
Drug	Atorvastatin	6.7	10.00
Carrier	Lactose 200 mesh	33.3	50.00
Vehicle	PEG 6000	44.0	66.00
Vehicle	Poloxamer 188	14.7	22.00
Excipient	Magnesium stearate	1.3	2.00
		100.0	150.00

CLAIMS

1. A single solid dosage form for oral administration comprising a first solid pharmaceutical composition containing fenofibrate as the active substance and second solid pharmaceutical composition containing an HMG-CoA reductase inhibitor as the active substance, wherein the first and the second pharmaceutical composition are present in separate entities.

2. The dosage form according to claim 1, wherein the HMG_CoA reductase inhibitor is a statin selected from the group consisting of atorvastatin, lovastatin, pravastatin, simvastatin, rosuvastatin, fluvastatin and pitavastatin.

3. The dosage form according to claim 1, wherein the first solid pharmaceutical composition is in the form of granulate, granules, grains, beads or pellets.

4. The dosage form according to claim 1, wherein the second solid pharmaceutical composition is in the form of granulate, granules, grains, beads or pellets.

5. The dosage form according to claim 4, wherein the granulate, granules, grains, beads or pellets are entero-coated.

6. The dosage form according to claim 4, wherein the granules, granulate, grains, beads or pellets are coated with a protective coating.

7. The dosage form according to claim 1, which is a capsule or a sachet.

8. The dosage form according to claim 1, which is a tablet.

9. The dosage form according to claim 8, in which the first and second pharmaceutical compositions are present in at least two separate layers.

10. The dosage form according to claim 9, wherein the layers comprising the first and second pharmaceutical compositions are separated by an intermediate, inactive layer.

11. The dosage form according to claim 1, which is a tablet prepared by compressing the first pharmaceutical composition in the form of granulate together with the second pharmaceutical composition in the form of granulate having a protective coating.

12. The dosage form according to claim 1, which is a tablet prepared by compressing the first pharmaceutical composition in the form of granulate together with the second pharmaceutical composition in the form of entero-coated granulate.

13. A method for preparing a single solid dosage form comprising a first solid pharmaceutical composition containing fenofibrate as the active substance and second solid pharmaceutical composition containing an HMG-CoA reductase inhibitor as the active substance, the first and the second pharmaceutical composition being present in separate entities, which method comprising the steps of:

i) preparing the first solid pharmaceutical composition,

ii) preparing the second solid pharmaceutical composition, and

iii) compressing the first and second compositions into a multilayer tablet, the first and second compositions being present in separate layers.

00104-DK01

ABSTRACT

A STABLE SOLID DOSAGE FORM COMPRISING FENOFIBRATE AND AN HMG COA REDUCTASE INHIBITOR

A single solid dosage form for oral administration comprising a first solid pharmaceutical composition containing fenofibrate as the active substance and second solid pharmaceutical composition containing an HMG-CoA reductase inhibitor as the active substance, wherein the first and the second pharmaceutical composition are present in separate entities. For example a multilayer tablet or capsules or sachets containing two separate granulates, the granulate comprising the second composition optionally being coated with a protective coating or an entero-coating.